Communication

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Attention should be paid to acute hepatitis of unknown etiology in children

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SUMMARY Since April 5, 2022, an increase in cases of severe acute hepatitis of unknown etiology among children with no underlying conditions was first reported in the United Kingdom (UK). Testing excluded viral hepatitis types A, B, C, D, and E and other known common and uncommon infectious and non-infectious causes of acute hepatitis. As of May 26, 2022, 650 cases of acute hepatitis of unknown etiology in children have been reported in at least 33 countries worldwide, with 99 additional cases pending classification. Here, the current prevalence of this condition around the world, a hazard analysis, possible causes, the risk of an outbreak in China, and advice on prevention have been briefly reviewed.

Keywords adenovirus infection, viral hepatitis, healthy children, acute hepatitis of unknown etiology in children, epidemic

1. Introduction

Since January 2022, cases of acute hepatitis of unknown etiology in previously healthy children have been reported in Europe, the USA, Japan and other regions and countries, causing widespread concern around the world. These cases excluded hepatitis viruses A, B, C, D, and E and other known common and uncommon infectious and non-infectious causes of acute hepatitis (*1,2*). There is no standard term for these cases of hepatitis. Here, the term "acute hepatitis of unknown etiology in children" as recommended by the World Health Organization (WHO) has been adopted. The current prevalence of this condition around the world, a hazard analysis, possible causes, the risk of an outbreak in China, and advice on prevention have been briefly reviewed.

2. Global epidemic situation

On April 5, 2022, there were reports of 10 cases of severe acute hepatitis of unknown etiology in children in the United Kingdom, and these cases involved children < 10 years of age. As of May 26, 2022, 650 cases of acute hepatitis of unknown etiology in children have been reported in at least 33 countries worldwide, with 99 additional cases pending classification (*3*). Compared to the last notification by the WHO on April 23, 2022, the number of cases increased from 169 to 650, and the number of countries reporting cases increased from 22 to 33. Of 650 probable cases, 222 (34.2%) were reported in the UK, the first country where they were reporter. Two hundred and sixteen cases (33.2%) were reported in the United States. In addition, Japan has reported 31 cases, which is the most in Asia. Canada has reported 10 cases and Mexico has reported 10 cases as well. Of the 33 countries that reported cases, 22 (66.7%) are in Europe, where 374 cases were reported. Other European countries besides the UK that have reported high numbers of cases include: Spain (29 cases), Italy (27), Belgium (14), the Netherlands (14), Portugal (11), Sweden (9), and Ireland (7) (Figures 1 and 2).

Of the 650 cases of acute hepatitis of unknown etiology in children, children in 9 cases (1.38%) died. At least 38 children (5.85%) required a liver transplant. The majority of reported cases (n = 490; 75.4%) involve children under 5 years of age. Of 156 patients on which information is available, 22 were critically ill and admitted to the ICU and 14 underwent a liver transplant.

As of June 9, 2022, 402 cases have been reported in Europe according to the European Centre for Disease Prevention and Control (ECDC). Cases were reported in the United Kingdom (224), Spain (36), Italy (31), Belgium (14), the Netherlands (14), Portugal (15), Sweden (9), Ireland (13), Poland (8), Denmark (7), France (7), Greece (6), and Norway (5) (*4*). No cases have been reported in China to date (Figure 3).

Epidemiologically, the vast majority of reported cases are unrelated. Moreover, there were no familial clusters

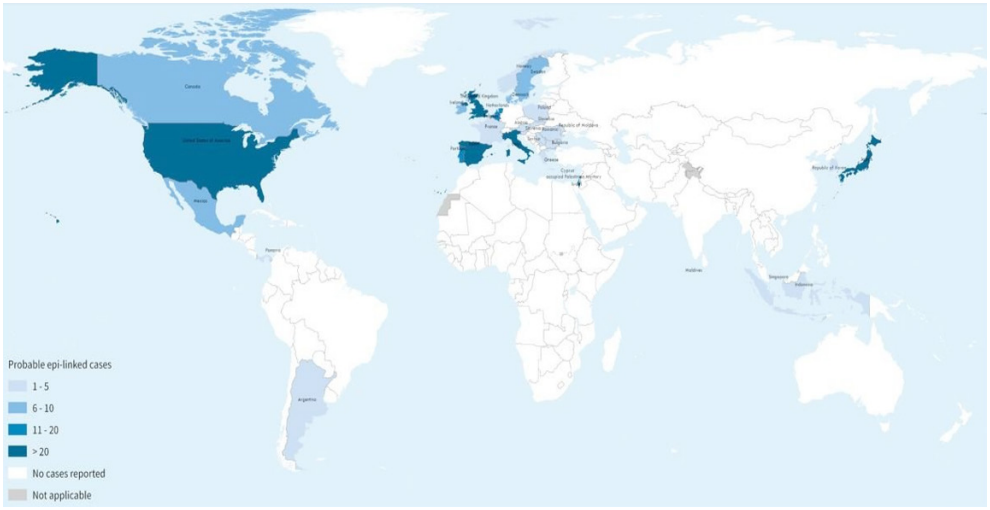

Figure 1. Distribution of probable cases of acute hepatitis of unknown etiology in children by country in five WHO Regions as of May 26, 2022 (*n* = 650). From the WHO.

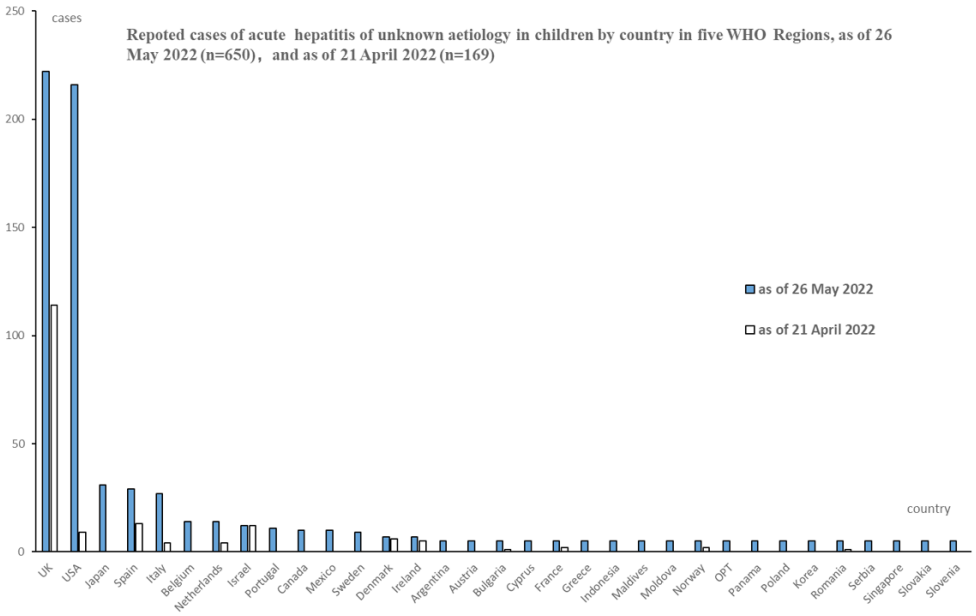

Figure 2. Reported cases of acute hepatitis of unknown etiology in children by country in five WHO Regions as of May 26, 2022 (*n* = 650) and as of April 21, 2022 (*n* = 169). From the WHO.

of the condition. The children were reported in different countries, and no travel history associated with the cases was noted. At present, most cases reported worldwide are sporadic, with no clusters or evidence of human-to-human transmission of infection. Although the risk at the global level was assessed as moderate, the WHO does not recommend travel restrictions for countries with cases (*3*).

3. Hazard analysis

The clinical characteristics of acute hepatitis of unknown etiology in children are as follows: An age of onset ranging from 1 month to 16 years of age, being previously healthy, and mostly involving children under 5 years of age. The main manifestations the condition include nausea, vomiting, diarrhea, jaundice, pale stool, and drowsiness. A fever has been noted in a few cases, most patients have no respiratory symptoms, ALT and AST levels are higher than 500 IU/L (higher than 2000 IU/L in some cases), and most cases have a good prognosis, but a few children develop liver failure and require a liver transplant (*3,5,6*).

There have been sporadic cases of acute hepatitis of unknown cause in children in the past, but the reason why this condition has aroused global attention now is because: 1) The number of children with acute hepatitis of unknown etiology and the number of countries reporting cases have increased rapidly in a short period of time. For example, only 169 cases were reported in 22 countries on April 23, 2022, while 650 cases were reported in 33 countries on May 26, 2022. Moreover,

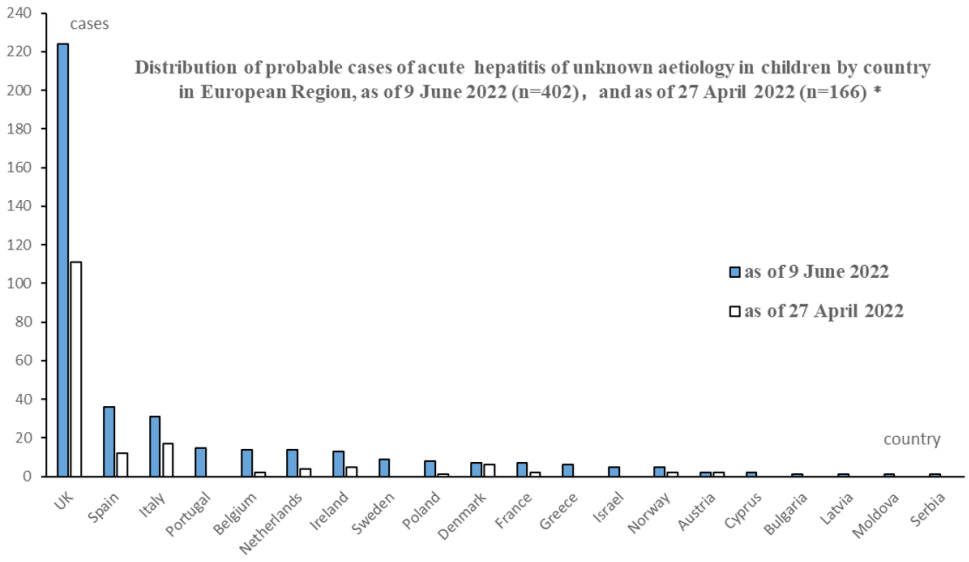

Figure 3. Reported cases of acute hepatitis of unknown etiology in children by country in European Region as of June 9, 2022 (*n* = 402) and as of April 27, 2022 (*n* = 166). From the ECDC. *Cases in the UK as of April 20, 2022.

due to the limited capacity to monitor the condition in some countries and regions, the true number of cases may be underestimated. 2) Compared to the previously reported cases of acute hepatitis of unknown etiology in children, cases being reported now are clinically severe, with a higher proportion of patients developing acute liver failure, requiring a liver transplant, and having a higher mortality. 3) The etiology is unknown, precluding assessment of the potential for further transmission. 4) This condition appeared during the COVID-19 epidemic and an association with SARS-CoV-2 cannot be completely ruled out. 5) Children have a limited ability to defend against disease, and this is particularly true for children under 5 years of age. Children are known to have a more limited organ reserve than adults; their condition changes rapidly and illnesses are more likely to be fatal. 6) Thus far, clusters of cases have not been noted, but human-to-human transmission cannot be completely ruled out yet. Therefore, attention should be paid to acute hepatitis of unknown etiology in children.

4. Possible causes

The exact etiology is unknown, and hepatitis viruses A, B, C, D, and E were excluded in these cases. According to the ECDC, specimens were collected in 293 cases and tested for adenovirus, of which 158 (53.9%) were positive. A total of 273 children with acute hepatitis of unknown cause were identified by PCR for SARS-COV-2, of which 29 (10.6%) tested positive. Serological tests for SARS-COV-2 were performed in 47 cases, of which 30 (63.8%) were positive (*3*). To the extent known, adenoviruses mainly cause respiratory infections and rarely cause severe acute hepatitis. According to the ECDC, an infectious agent (including adenovirus or a novel variant adenovirus or a new variant of SARS-CoV-2 or other pathogen) remains the most plausible cause, but a drug, a toxin, environmental exposure, *etc*. cannot be completely ruled out (*7*). Many children under the age of 10 in Europe have not been vaccinated against COVID-19, so acute hepatitis of unknown etiology in children is not considered to be related to COVID-19 vaccine so far.

Since liver biopsy specimens were not pathologically diagnosed in most cases, there is no direct grounds for considering the condition to be adenovirus hepatitis. Therefore, a confirmed diagnosis of adenovirus hepatitis based only on test results of specimens from the respiratory tract, digestive tract, and blood is difficult. Previously, the majority of confirmed cases of adenovirus hepatitis have been reported in immunocompromised or immunosuppressive adults, such as patients with lymphoma or patients receiving immunosuppressive agents while undergoing a liver transplant (*8-10*). In those cases, a liver biopsy was pathologically diagnosed, *e.g*., electron microscopy of biopsied liver tissue revealed adenovirus particles.

There are a few cases of acute hepatitis caused by adenovirus in children in the literature, where adenovirus hepatitis was confirmed by pathological results of a liver biopsy. In Canada, a 20-month-old boy with atypical malformed rhabdomyoma (ATRT) underwent a liver biopsy after admission. Adenovirus hepatitis was confirmed when electron microscopy revealed adenovirus particles, and the patient was positive for adenovirus according to PCR (*11*). A liver biopsy is difficult to perform in children because they are not as capable of tolerating the procedure as adults and they cannot hold their breath.

In addition to adenoviruses, Epstein-Barr viruses, enteroviruses, rhinoviruses, metapneumoviruses, and respiratory syncytial viruses were also reported

to associated with hepatitis in children (*13*). Other rare pathogens causing hepatitis in children include human parvovirus B19, rotavirus, Boca virus, respiratory envelope virus, cytomegalovirus, varicella-zoster virus, and measles virus (*13-18*). In addition to microbial pathogens, other conditions that cause hepatitis in children include Wilson's disease, hereditary hemochromatosis (HH), hereditary hyperbilirubinemia, an α-1 antitrypsin deficiency, drug-induced liver failure, Reye syndrome, cystic fibrosis, Alagille syndrome, and tyrosinemia type I, *etc*..

5. Risk assessment in China

Based on the currently available information, an outbreak of acute hepatitis of unknown etiology in children in China is unlikely in the short term. Possible reasons for this may be: 1) Current epidemiological data have revealed no evidence of human-to-human transmission, with 650 cases distributed across 33 countries; 2) China's strict and scientific COVID-19 epidemic prevention policy ensures that imported cases are prevented. Chinese Customs will continue to take strict measures to ensure entry-exit health quarantines, enhance multi-department joint prevention and control, and strictly prevent the risk of imported epidemics. 3) Good hand hygiene, wearing masks, etiquette when coughing, social distancing and other measures to combat COVID-19 have been well understood and implemented by the general public. Common respiratory infections in children, as an example, have been significantly reduced since the implementation of COVID-19 prevention policies in China. At present, China's experience with the prevention and control of COVID-19 and improvements in public health awareness have greatly helped to prevent acute hepatitis of unknown etiology in children. 4) Practice has proven that the dynamic zero-COVID approach safeguards people's health best. These epidemic prevention policies are conducive to the prevention and control of acute hepatitis of unknown etiology in children. However, the possibility of acute hepatitis of unknown cause in children appearing in China in the future cannot be completely ruled out.

6. Advice on prevention and control

Although an outbreak of acute hepatitis of unknown cause in children in China is unlikely in the short term, physicians still need to be vigilant and pay close attention to WHO and ECDC reports. According to the recommendations of the Chinese Health Commission, the following preventive measures should be taken: 1) Children should avoid going to crowded public places with poor ventilation, and droplet contact and fecal-oral transmission should be interrupted; 2) Children should receive adequate sleep and nutrition; 3) Children's outdoor clothes and objects they regularly touch should be washed, they should wear a mask, and they should practice good hand hygiene and maintain social distancing. In addition, children with symptoms such as vomiting and diarrhea should stay at home for 48 hours until symptoms disappear before returning to school or kindergarten. Healthcare workers, and especially pediatric medical staff, should be on high alert for clinical symptoms of hepatitis in children. Suspected cases of acute hepatitis of unknown etiology in children should be reported to the Centers for Disease Control (CDC) as soon as possible and affected children should be sent to the hospital for testing to promptly identify the cause of hepatitis. Health authorities should assemble experts to study and discuss prevention and treatment strategies and to formulate guidelines to facilitate diagnosis, case investigation and reporting, and clinical management of acute liver failure in children. Health authorities should be prepared for any possible outbreak.

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